REMARKS

A. Status of the Claims

Claims 80-88 are amended. Therefore, claims 80-88 are pending with entry of this amendment.

B. Specification

The specification has been amended to specify the Government's interest in the current invention in accordance with 37 C.F.R. §401.14(f)(4).

C. Written Description

Claims 80-88 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Specifically, the Examiner asserts that the specification fails to provide support for the phrase "ligand activated uni-molecular sensor." In addition, the Examiner alleges that the specification does not provide a representative number of examples to indicate to one skilled in the art that Applicants were in possession of the claimed invention at the time of filing. In light of the amendments to the claims and the remarks presented below, Applicants respectfully disagree.

1. "Ligand Activated Uni-Molecular Sensor"

The law is clear that it is ***not necessary*** that the specification describe claim terms ***exactly***, but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that appellants invented the composition including those terms. *See In re Wertheim*, 191 USPQ 90, 96 (CCPA 1976); *Ralston Purina Co. v. FarMar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985), stating that the test for support of the subject matter of a claim is whether the disclosure of an application "reasonably conveys to the art isan that the inventor had possession at that time of the later claimed subject matter" (quoting *In re Kaslow*, 217 USPQ 1089, 1096 (Fed. Cir. 1983)). In addition, the MPEP explicitly recognizes the principle that the "subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." *See* MPEP §2163.02.

Applicants respectfully submit that the specification provides support for the phrase "ligand-activated uni-molecular detector" in compliance with 35 U.S.C. § 112, first paragraph. As pointed out in Applicants' Amendment dated August 26, 2003, support for the phrase "ligand-activated uni-molecular detector" may be found, for example, on page 7, lines 19-25, stating, in part:

> ***Ligand-activated*** or interaction-activated ***CPs*** are advantageously used over interaction-dependent fragment complementation systems for certain assays, in that they exhibit lower order kinetics of activation, i.e., ***uni-molecular*** instead of bi-molecular for two-component interactions and bi-molecular instead of tri-molecular for three-component interactions (emphasis added).

Additional support may be found, for example, at page 11, lines 15-30. Thus, Applicants submit that the specification reasonably conveys to one of skill in the art that Applicants had possession of a ligand-activated uni-molecular detector at the time of filing.

However, to expedite prosecution, Applicants have substituted the phrase "ligand-activated uni-molecular detector" with the term "polypeptide" in claims 80-88. Support for the term "polypeptide" may be found, for example, at page 12, lines 14-20, stating in part, "[a] circular permutation interaction-dependent enzyme activation system involves the expression of a single fusion polypeptide that comprises in the direction of translation, a first interactor domain that is in frame with a circularly permutated marker protein that is in frame with a second interactor domain." See also page 6, lines 12-19. Therefore, no new matter is added with this amendment.

2. The Specification Establishes Possession of the Claimed Invention in Compliance with 35 U.S.C. § 112, Second Paragraph

The Examiner asserts that, although the specification provides seven working examples that meet all the limitations of the claimed invention, the specification fails to comply with the written description requirement.

a) The Law Regarding the Written Description Requirement

To satisfy the written description requirement, a patent specification must merely describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *See Lockwood v. American Airlines, Inc.*, 41 USPQ2d 1961, 1966 (1997). *See also Vas Cath, Inc. v. Mazurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991).

Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations, as set forth in the MPEP. For example, at §2163(II)(A)(2), the MPEP states that the knowledge and skill in the art should be considered:

> The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention. Such a review is conducted from the standpoint of one of skill in the art at the time the application was filed ... and should ***include a determination of the field of the invention and the level of skill and knowledge in the art.*** Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement (emphasis added).

At §2163(II)(A)(3)(a), the MPEP states that other factors, such as partial structures and sequences should be taken into account:

> An applicant may also show that an invention is complete by disclosure of . . . complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known of disclosed correlation between function and structure, or some combination of such characteristics. *Enzo Biochem*, 63 USPQ2d at 1613 . . . For some biomolecules, examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular weight, and length.

The MPEP mirrors the CAFC decision in *Enzo*. *See Enzo Biochem Inc. v. Gen-Probe Inc.*, 63USPQ2d 1609, 1613 (Fed. Cir. 2002). In *Enzo*, the Federal Circuit held that the written description requirement for functional claim descriptions is satisfied when the functional characteristics are coupled with a disclosed correlation between that function and a structure that is "sufficiently known or disclosed." *Enzo*. at 1613. Thus, both the Federal Circuit and the USPTO are clear that the raw number of working examples is only one factor in determining whether claims comply with the written description requirement. In addition to the number of working examples, other factors to be considered include: any partial structures provided in the claims, knowledge in the art regarding the correlation between structure and function, and methods of making the claimed invention provided in the specification.

Moreover, the Federal Circuit has determined that the number of working examples required to provide adequate support for broad composition claims may be very low. For example, the patent at issue in *Enzo* was directed to nucleic acid sequences that preferentially hybridize to the chromosomal DNA of *Neisseria gonorrhea* over *Neisseria meningitidis*. The patentee disclosed only ***three*** operative nucleic acid sequences which hybridized to only ***six*** strains of *Neisseria gonorrhea*. The patentee sued two of its competitors for infringement, and the defendants moved for summary judgment on the ground that the claims were invalid for failure to meet the written description requirement. The district court granted the motion, concluding that the claimed composition of matter was defined only by its biological function, which it deemed insufficient to satisfy § 112, P 1. The Federal Circuit reversed summary judgment, finding that genuine issues of material fact existed regarding satisfaction of the written-description requirement. Thus, the Federal Circuit refused to uphold summary judgment under § 112, P 1 invalidating a claim for functionally describing ***all*** nucleic acid probes that bind to ***any*** strain of *Neisseria gonorrhea* where the specification set forth only ***three*** operative nucleic acid probes that hybridize to only ***six*** strains of *Neisseria gonorrhea*.

In reversing the district court, the Federal Circuit in *Enzo* distinguished its earlier decision in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). In *Lilly*, the Federal Circuit determined that a disclosure of a ***single*** rat cDNA was not descriptive of a broad claim encompassing mammalian and vertebrate cDNA. *See Enzo* at 1615, citing *Lilly*

at 1405. The *Enzo* court pointed out that, in *Lilly*, the disclosure of a ***single*** rat cDNA failed to "describe a sufficient number of species within the very broad genus to indicate that the inventors had made a generic invention, i.e., that they had possession of the breadth of the genus, as opposed to merely one or two such species." *See Enzo* at 1615.

Therefore, according to the Federal Circuit, disclosure of ***three*** nucleic acid sequences that preferentially hybridize to **six** strains of *Neisseria gonorrhea* may be a sufficient correlation between structure and function to claim ***all*** nucleic acid sequences that preferentially bind to ***any*** strain of *Neisseria gonorrhea*. However, disclosure of a ***single*** rat cDNA is not sufficient to claim a genus of compounds encompassing mammalian and vertebrate cDNA.

In *University of Rochester v. G.D. Searle & Co.*, the U.S. District Court for the Western District of New York applied the guidelines relating to nucleic acid composition claims set forth by the Federal Circuit in *Enzo* and *Lilly* to claims covering a method of selectively inhibiting an enzyme using a pharmaceutical agent. *See University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 (W.D.N.Y. 2003). The patent at issue claimed a "method for selectively inhibiting PGHS-2 [mammalian prostaglandin H synthase-1] activity in a human host" using a "non-steroidal compound" in which "the activity of PGHS-1 is not inhibited." *See Rochester* at 1426.

The district court repeated the standard set forth by the Federal Circuit in *Enzo*, stating "the written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics,' including, *inter alia*, 'functional characteristics when coupled with a known or disclosed correlation between function ad structure.'" *Id.* at 4129. However, because the specification did not set forth "***so much as one compound*** that would be suitable for use in practicing the claimed invention," the district court granted summary judgment invalidating the claims for failing to fulfill the written description requirement. *Id.* at 1431 (emphasis added). The Federal Circuit has recently upheld the district court's decision in *Rochester*. *See University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004). The court reaffirmed that the written description is a separate requirement, which applies to all types of inventions, including non-genetic materials and method claims. *Id.* at 1891, 183.

Thus, it is apparent from *Enzo*, *Lilly*, and *Rochester* that the written description standard may be met for broad composition claims by disclosing as few as ***three*** operable structures. *See Enzo* at 1613. Applicants respectfully assert that, in light of the Federal Court decisions outlined above, the ***seven*** working examples disclosed in the current specification is more than adequate to meet the written description standards set forth by the Federal Circuit and the USPTO. Moreover, Applicants have also provided substantial guidance in the specification regarding methods of designing, making and testing the claimed polypeptides (see below).

In addition to the case law outlined above, it is well established that the examiner "has the initial burden of presenting evidence or reasons why persons of skilled in the art would not recognize in the disclosure a description of the invention defined by the claims." See *In re Wertheim*, 191 USPQ 90, 97 (CCPA 1976). Therefore, where the specification provides an actual reduction to practice of a process that meets all the limitations of the claim thereby demonstrating that the invention works for its intended purpose, the Examiner must present evidence as to why one skilled in the art would not reasonably conclude that the inventor was in possession of the claimed method. See MPEP §2163 II.A.3.(a).

b) Claims 80-88 as Amended Comply with the Written Description Requirement

The Examiner asserts that claim 80 is overly broad because the claim encompasses "open ended" compositions. *See* Official Action of May 5, 2004, page 6, first full paragraph. In response, Applicants have deleted the open-ended term "comprising" with the phrase "consisting essentially of." Applicants note that according to the MPEP, "[t]he transitional phrase 'consisting essentially of' ***limits*** the scope of a claim to the specified materials or steps 'and those that do not materially affect the basic and novel characteristic(s)' of the claimed invention [quoting *In re Herz*, 537 F.2d 549 (CCPA 1976)(emphasis added)."

The Examiner further asserts that the use of the phrase "consisting essentially of" in claim 85 results in overly broad claims encompassing undisclosed analogs of SEQ ID NO: 2. In response, Applicants have deleted the phrase "consisting essentially of" from claim 85. Therefore, the polypeptide of claim 85 encompasses ***only*** those compositions containing the recited circularly permutated sequence.

In light of the amendments to claims 80 and 85, Applicants submit that the currently pending claims comply with the written description requirement. Moreover, one skilled in the art would reasonably conclude that the Applicants were in possession of the claimed invention based on:

(1) the representative number of working examples;

(2) the knowledge in the art regarding circular permutation of proteins; and

(3) successful principles for designing interaction dependent circularly permutated proteins are disclosed in the specification.

(1) Working Examples

As mentioned above, where the specification provides an actual reduction to practice of a composition that meets all the limitations of the claim thereby demonstrating that the invention works for its intended purpose, the Examiner must present evidence as to why one skilled in the art would ***not*** reasonably conclude that the inventor was in possession of the claimed invention. See MPEP §2163 II.A.3.(a). Moreover, the Federal Circuit has determined that the written description standard may be met for broad claims by disclosing as few as ***three*** operable structures. See *Enzo Biochem Inc. v. Gen-Probe Inc.* at 1613.

Here, Applicants have provided ***seven*** working examples of polypeptides that meet the limitations set forth in claims 80-88. The disclosed working examples are set forth in Table 1 below.

Table 1

POLYPEPTIDE	LIGAND	SPECIFICATION
BW10-1-CP-p44-4-2	CD40	page 42, Table 4; page 71, line 26 to page 72, line 22
BW10-1-CP-fos	CD40-jun	page 42, Table 4; page 71, line 26 to page 72, line 22
fos-CP-p44-4-2	jun-CD40	page 42, Table 4; page 71, line 26 to page 72, line 22

scFv-CP-jun	CD40-fos	FIG 11; page 72, line 22 to page 77, line 16
CD40-CP-jun	scFv-fos	FIG 11; page 72, line 22 to page 77, line 16
fos-CP-CD40	scFv-jun	FIG 11; page 72, line 22 to page 77, line 16

In light of the diverse set of working examples disclosed above, Applicants respectfully submit that claims 80-88, as amended, comply with the written description requirement. Because the Examiner has not presented evidence as to why one skilled in the art would ***not*** reasonably conclude that the inventor was in possession of the claimed method based on these working examples, Applicants respectfully request withdrawal of the rejection.

(2) Knowledge in the Art Regarding Circular Permutation of Proteins

As discussed above, he knowledge and skill in the art should be considered determining whether there is sufficient evidence of possession. *See* §2163(II)(A)(3)(a).

It is well known that many circularly permutated proteins are capable of functionally reconstituting. For example, the specification states:

> Functional circular permutations have been described for green fluorescent protein (Baird, et al, *Proc Natl Acad Sci* (1999) 96:11241 and Topell, et al, *FEBS Lett* (1999) 457:283), disulfide oxidoreductase (Hennecke et al., *J Mol Biol* (1999) 286:1197), dihydrofolate reductase (Iwakura, *Biosci Biotechnol Biochem* (1998) 63:778), beta-glucosidase (Garcia-Vallve et al., *Proteins* (1998 31:214), beta-glucanase (Ay et al, *Proteins* (1997) 30:155), aspartate transcarbamoylase (Graf and Schachman, *Proc Natl Acad Sci* (1996) 93:11591), dihydrofolate reductase (Uversky et al., *Protein Sci* (1996) 5:1844), and phosphoglycerate kinase (Ritco-Vonsovici et al. *Biochemistry* (1995) 34:16543). In fact, active circular permutations occur naturally and may be common (*Lindgvist and Schneider*, Curr Opin Struct Biol (1997) 7:422; Jia et al., *Structure* (1996) 4:715). See page 66, lines 1-11.

Applicants note that the examples cited above are not capable of functionally reconstituting only upon binding of a first and second interactor domain as recited in claims 80-88. However, this passage is evidence of the knowledge in the art regarding the general ability of a diverse array of proteins to functionally reconstitute after circular permutation. Given the knowledge in the art regarding the diverse array of proteins able to reconstitute after circular permutation, coupled with the seven working examples disclosed in the specification, Applicants submit that the specification fully supports claims 80-88 as amended.

(3) The Specification Sets Forth Successful Principles for Designing Interaction Dependent Circularly Permutated Proteins

The specification provides extensive guidance to one skilled in the art regarding methods of designing, making and testing the polypeptides of claims 80-88. For example, on page 66, line 11 to page 67, line 31, the specification discloses:

> ...[I]t is reasonable to expect that most proteins will have one or more exposed loops whose integrity is essential for stability. This is supported by observations that cleavage of protease recognition sites inserted into exposed loops of (3-galactosidase (Baum el al., *Proc Natl Acad Sci* (1990) 87:10023) or the tetracycline resistance protein (Block and Grafstrom, *Anlimicrobial Agents and Chemotherapy* (1990) 34:2337) in many cases lead to inactivation of the enzymes. Thus, ***circular permutation of the polypeptide chain within such loops should produce unstable proteins***. This is the first of three requirements for an interaction-dependent CP. The second requirement is that ***the CP must not be sterically blocked from reaching the active conformation***. The third requirement is that in the equilibrium ensemble of inactive conformations of the CP ***the break-point termini are separated by an average distance which exceeds that allowed by interactions of heterologous domains fused to the break-point termini*** . . . Thus, in principle, useful interaction-dependent circular permutations should be possible if foldable, but unstable CPs can be found in which the average separation of the break-point termini is large . . . in the case of the CP, it is transient folding of the CP which allows the interactors to make contact, and the latter then traps the CP in an active

> conformation. To identify such CPs of TEM-1 β-lactamase we inserted a sequence encoding the flexible $(Gly_4Ser)_3$ linker between the C and N-termini of two tandem copies of the TEM-1 sequence. CPs of the TEM-1 sequence were then amplified by PCR using primers which terminated within each of ten different exposed loops in the structure of the enzyme (see Figure 3) (emphasis added).

From the above passage, one of skill will immediately realize that Applicants were in possession of concrete principles of identifying and producing interaction dependent circularly permutated proteins. Moreover, these principles were successfully employed to produce seven examples of interaction dependent circularly permutated proteins.

Combining these principles with the seven operative embodiments and the general knowledge in the art regarding the array of functionally reconstituting circularly permutated proteins, Applicants submit that one skilled in the art would immediately recognize that Applicants were in possession of the polypeptide encompassed by claim 80-88. Therefore, Applicants respectfully request withdrawal of the rejection.

D. Indefiniteness

The Examiner has rejected the claims as being indefinite for the use of the phrase "ligand activated uni-molecular detector" in claim 80, "consists essentially of" in claim 88, and "circularly permutated marker comprising" in claim 80. Applicants note that the terms "ligand activated uni-molecular detector" in claim 80, "consists essentially of" in claim 88, and "circularly permutated marker comprising" in claim 80 have been deleted. Therefore, Applicants respectfully request withdrawal of the rejection.

E. Cited Reference

The Examiner has rejected claims 80-88 as allegedly anticipated by Remy et al., Pieper et al., and Michnick et al. Applicants respectfully disagree.

It is well settled that "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." See MPEP § 2131 (quoting *Verdegaal Bros. v. Union Oil Co. of California*, 814

F.2d 628, 631 (Fed. Cir. 1987)). As discussed below, Remy et al., Pieper et al., and Michnick et al. do not describe the polypeptide of claim 80-88.

1. Remy et al. and Michnick et al. Do Not Anticipate the Claimed Invention

Remy et al. and Michnick et al. disclose a protein-fragment complementation assay ("PCA") in which the murine enzyme dihydrofolate reductase (DHFR) is split into two ***separate*** fragments. *See* Remy et al. at page 5394, column 1; page 5395, column 2. *See* Michnick et al. column 5, line 35 to column 6, line 67, Figures 1 and 2, and abstract. Each fragment is fused to separate protein domains which are thought to interact. Upon binding of the interacting protein domains, the DHFR fragments functionally reconstitute to from an active, detectable DHFR.

Applicants claims are drawn to an polypeptide having a circularly permutated marker protein. The circularly permutated marker protein is covalently bonded to a first interactor domain and a second interactor domain. As described in the specification and is well known in the art, a circularly permutated marker is a uni-molecular species. *See* page 7, lines 19-25, which is reproduced above. The circularly permutated marker protein is ***covalently bonded*** to a first interactor domain and a second interactor domain.

Therefore, the circularly permutated marker protein, first interactor domain, and second interactor domain is a ***single*** molecule. In contrast, the PCA system of Remy et al. and Michnick et al. consists of two ***separate*** fragments. Moreover, Remy et al. and Michnick et al. fail to disclose a circularly permutated marker protein that functionally reconstitutes only upon binding of the first interactor domain and the second interactor domain to a ***single ligand***. In fact, neither Remy et al. nor and Michnick et al. mention circularly permutated proteins at all, much less a circularly permutated β-lactamase protein of claims 82, 83, and 85.

Because Remy et al. and Michnick et al. fail to disclose an polypeptide having a single, circularly permutated marker protein that functionally reconstitutes upon interactor binding to a single ligand, claims 80-88 are not anticipated. Therefore, Applicants respectfully request withdrawal of the rejection.

2. Peiper et al. Does Not Anticipate the Claimed Invention

Peiper et al. merely discloses constitutively active circularly permutated β-lactamase compositions with no interactor domains. Applicants' claims encompass only those circularly permutated marker proteins that are covalently bound to a first and second interactor domains. The circularly permutated marker protein is functionally reconstituted only upon binding of the first interactor domain and the second interactor domain to a single ligand.

Because Peiper et al. fails to disclose circularly permutated marker proteins that are covalently bound to a first and second interactor domain, claims 80-88 are not anticipated. Therefore, Applicants respectfully request withdrawal of the rejection.

F. Double Patenting

Claims 80-88 were provisionally rejected under the judicially created doctrine of double patenting as allegedly being obvious over claims 63-66 of co-pending U.S. Application No. 09526106.

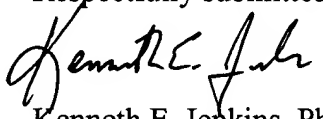
Applicants respectfully request that this rejection be held in abeyance until patentable subject matter has been found. At that time, Applicants will take the necessary steps to obviate the double patenting rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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